CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 2, 2011
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Irene Z. Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Docefrez (Docetaxel) for Injection 20 mg per vial and 80 mg per vial
Application Type/Number:	NDA 022534
Applicant:	Sun Pharma Global FZE
OSE RCM #:	2011-313

MEMO TO FILE

Sun Pharma Global FZE submitted revised container labels, carton labeling, and Dear Healthcare Professional (DHCP) letter on April 29, 2011, that incorporated all of DMEPA's previous recommendations. We find the revised container labels and carton labeling acceptable; however, we do have two additional recommendations for the DHCP letter as follows:

1. Under A.1. revise [redacted] to "46ºF" so that it matches the insert labeling.
2. In the last paragraph of the letter, revise the second sentence to read "If you need further information about this product, please contact our distributor Caraco Pharmaceutical Laboratories, Ltd at 1-800-818-4555."

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

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/s/

LORETTA HOLMES
05/02/2011

IRENE Z CHAN
05/02/2011

CAROL A HOLQUIST
05/02/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 5, 2011
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Irene Z. Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Docefrez (Docetaxel) for Injection
Application Type/Number:	NDA 022534
Applicant:	Sun Pharma Global FZE
OSE RCM #:	2011-313

1 INTRODUCTION

This review evaluates the revised labels and labeling for Sun Pharma Global's Docefrez submitted on October 19, 2010 for areas of vulnerability that could lead to medication errors. This review is written in response to a request from the Division of Drug Oncology Products.

1.1 REGULATORY HISTORY

This NDA is a 505(b)(2) application. The Reference Listed Drug is Taxotere (Docetaxel) Injection Concentrate, NDA 020449. This NDA was tentatively approved on February 23, 2010. On October 19, 2010, Sun Pharma requested final approval of this NDA after a favorable court ruling concerning patent infringement.

DMEPA completed a label and labeling review of Docefrez in OSE Review 2009-983, dated February 19, 2010. All of our labeling comments were communicated to the Applicant and revised labels and labeling were submitted on February 22, 2010. DMEPA found those revisions to the labels and labeling acceptable. The Applicant submitted revised labels and labeling in the October 19, 2010 request for final approval.

1.2 BACKGROUND ON DOCETAXEL PRODUCTS

Taxotere, a Sanofi Aventis product, was approved on May 14, 1996, as a two-vial configuration consisting of one vial of active drug solution (40 mg/mL) and one vial of diluent that must be mixed together to yield a concentration of 10 mg/mL before being added to the infusion solution. The two-vial configuration has undergone numerous label and labeling changes in addition to educational interventions to address medication errors that resulted from confusion with the unusual two-step dilution.

On August 2, 2010, a new one-vial formulation of Taxotere was approved by the FDA. This one-vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one-vial formulation was approved with a concentration of 20 mg/mL.

On March 8, 2011, a 505(b)(2) application for Docetaxel Injection, manufactured by Hospira, was approved by the FDA. The Docetaxel Injection by Hospira is also a one-vial formulation like the one-vial formulation of Taxotere. An important difference between these two products is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's one-vial formulation of docetaxel is available in a concentration of 10 mg/mL. The reference listed drug for Hospira's product is Taxotere. Since approval, we have received complaints concerning this disparity in concentrations.

(b) (4)

(b) (4) Docefrez is a powder for injection that when reconstituted has a concentration that differs from all the other approved (b) (4) docetaxel products.

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1.3 PRODUCT INFORMATION FOR DOCEFREZ

Docefrez for Injection is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, and hormone refractory prostate cancer. Docetaxel has a boxed warning concerning toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. The dosing regimens vary depending on the indication of use (see Appendix A). Docefrez must be reconstituted with the supplied diluent. Once reconstituted, the 20 mg vial yields a concentration of 20 mg/0.8 mL and the 80 mg vial yields a concentration of 24 mg/mL. The required amount of Docefrez solution is then withdrawn from the vial(s) and added to the infusion solution. The solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered intravenously through polyethylene-lined administration sets over one hour.

Docefrez will be supplied in 20 mg and 80 mg strengths. Docefrez and the diluent will be packaged in a tray in one carton.

2 METHODS AND MATERIALS

DMEPA previously conducted an AERS search to identify medication errors involving Taxotere or docetaxel (see OSE review 2007-548 dated March 23, 2007). Results of the previous search were used to inform label and labeling recommendations for Taxotere two-vial formulation in order to minimize medication errors that were occurring at that time. Since 2007, an updated search for docetaxel medication errors has not been completed. Given the changes to the labels and labeling for Taxotere since 2007, the multiple pending applications, and complicated safety issues concerning docetaxel products, DMEPA conducted a new search of the FDA Adverse Event Reporting System (AERS) database. We also reviewed a medication error report from the Institute for Safe Medication Practices (ISMP). The proposed labels and labeling were reviewed as well.

2.1 AERS SELECTION OF CASES

An AERS search was conducted on March 21, 2011 using the MedDRA High Level Group Terms "Medication Errors" and "Product Quality Issues", active ingredient "Doce%", trade name "Taxo%", and verbatim "Taxo%" and "Doce%". The search was limited to the dates March 23, 2007 through March 21, 2011. This time period covers the time since our last AERS search conducted for OSE Review 2007-548.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If the root cause(s) could be associated with the labels, labeling, or packaging of the product, the cases were considered pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse drug event not resulting from a medication error, product quality complaints, etc.), were excluded from further analysis.

2.2 ISMP MEDICATION ERROR REPORT

The article "Dosing error with the new Taxotere concentration" in the March 24, 2011 issue of ISMP Medication Safety Alert[1] was reviewed.

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[1] "Dosing error with new Taxotere concentration," *ISMP Medication Safety Alert*, Vol. 16, Issue 6, March 24, 2011.

Reference ID: 2928541

2.3 LABEL AND LABELING RISK ASSESSMENT

DMEPA uses Failure Mode and Effects Analysis (FMEA) and lessons learned from post-marketing experiences to evaluate container labels, carton and insert labeling. This review summarizes our evaluation of the container labels and carton labeling submitted by the Applicant on October 19, 2010 (see Appendices D through F).

- Container Labels (active drug and diluent), 20 mg and 80 mg
- Carton Labeling (carton contains active drug plus diluent), 20 mg and 80 mg

We reserve review of and recommendations for the insert labeling for the labeling meetings scheduled with the Division of Drug Oncology Products. Our recommendations will be made to the working insert labeling that is available on the shared (N) drive.

3 RESULTS AND DISCUSSION

The following sections describe the findings and assessment of the AERS data, ISMP medication error report, and the label and labeling review.

3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES

The AERS search conducted on March 21, 2011, retrieved 26 cases (see Appendix B for ISR numbers). Of the 26 cases, 23 were excluded (see Appendix C). Thus, three reports remained for our evaluation:

Potential Error (n=2)

- The reporter stated the product packaging of Taxotere is confusing because the 80 mg/2 mL active drug plus the 7.1 mL of diluent adds up to 9.1 mL, not the 80 mg/8 mL needed for a 10 mg/mL concentration. The reporter further explained that this could lead to errors if a person didn't closely read the entire box prior to final product preparation. (ISR #5581415)
- The reporter stated the concentration of the new Taxotere [one-vial] formulation (20 mg/mL) could cause an overdose because this is an increase from the two-vial Taxotere which is 10 mg/mL after the initial dilution step. (ISR #7092480)

Improper Dose or Wrong Technique (n=1)

- The reporter stated students made 3 doses of Taxotere incorrectly, all of which were caught prior to patient administration. The details of the error were not reported; therefore, it is difficult to determine whether an improper dose was made or if wrong technique was used in preparing the doses (ISR # 5403737).

Our AERS results indicate there is still confusion with the two-vial formulation of Taxotere between the concentration of the active drug vial and the resultant concentration after the initial dilution step. The concentration of the active drug is necessary on the vial label in order to inform healthcare practitioners of its contents. Additionally, it is due to the physical characteristics of the product that the volume of active drug plus the volume of diluent, when they are combined, do not add up to the expected volume. This is explained in the insert labeling, and it is not feasible to put all of this additional information on the container labels and carton labeling due to space limitations. However, the instructions for preparation are highlighted on the container labels and carton labeling so that they are readily available and if they are read, the product can be prepared correctly. We will ensure this is included for the container labels and carton labeling for Docetaxel Injection.

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DMEPA is aware that the Taxotere one-vial formulation (20 mg/mL) (b) (4) may cause confusion that can lead to medication errors due to differences in concentration and preparation instructions from the two-vial formulation. Additionally, Hospira's one-vial formulation for Docetaxel Injection (10 mg/mL) compounds the confusion because its concentration is different from one-vial Taxotere. We make recommendations in section 4 below based on previous recommendations implemented for other docetaxel products to minimize the risk of confusion.

3.2 ISMP MEDICATION ERROR REPORT

ISMP published a report dated March 24, 2011, that described a medication error in which a patient on Taxotere received twice the intended dose 100 mg/m^2 rather than the reduced dose of 50 mg/m^2. This error occurred soon after an ambulatory cancer center pharmacy began to transition from the two-vial Taxotere which yields a concentration of 10 mg/mL after initial dilution to the new one-vial Taxotere which has a 20 mg/mL concentration. The physician ordered 50 mg/m^2 and although the dose administered was 100 mg/m^2 which is within safe dosing limits, the patient suffered febrile neutropenia which necessitated hospitalization. There are a number of factors that could lead to such an error including long-time familiarity with the two-vial Taxotere formulation, confirmation bias, delays in updating computer software to reflect the new concentration, stocking of both products concurrently, calculating the dose based on the 10 mg/mL concentration but using the 20 mg/mL concentration to prepare the infusion, and lack of knowledge regarding the new concentration of Taxotere.

3.3 LABEL AND LABELING RISK ASSESSMENT

The following deficiencies were noted in the container labels and/or carton labeling:

- (b) (4)
- There is a lack of statements that highlight and caution healthcare providers about the product concentration.
- There are statements on the labels and labeling that are not optimally positioned.

Due to the availability of multiple formulations in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

- One-vial vs. two-vial formulations
- Concentration of 10 mg/mL or 20 mg/mL vs. concentration of 20 mg/0.8 mL or 24 mg/mL prior to dilution in infusion bag

We provide recommendations for color changes and other revisions that we believe will help to minimize the potential for confusion between the varying formulations, concentrations, and preparation instructions among the different docetaxel products in Section 4 below.

Additionally, due to the fact that reconstituted Docefrez has a concentration that will differ from all of the currently marketed products, we anticipate this will lead to medication errors. Thus, a communication such as a Dear Healthcare Provider letter that explains the differences between

Docefrez and the currently marketed products may help to alert healthcare providers to the new dosage form and concentration.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation identified areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. Section 4.1 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

4.1 COMMENTS TO THE APPLICANT

A. General Comment for the Container Labels, Diluent Labels and Carton Labeling

Due to the availability of multiple formulations of docetaxel in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

- One-vial vs. two-vial formulations
- Concentration of 10 mg/mL or 20 mg/mL vs. concentration of 20 mg/0.8 mL or 24 mg/mL prior to dilution in infusion bag

(b) (4)

[redacted]

B. General Comment on Product Design

Docefrez is a powder and as such the dosage form differs from the currently marketed docetaxel products. Additionally, once Docefrez is reconstituted, the concentration differs from the currently marketed docetaxel products. Thus, we anticipate medication errors will occur with the use of Docefrez.

Therefore, at the time of product launch, DMEPA recommends you inform healthcare practitioners about the differences in the preparation of Docefrez as compared to the

Reference ID: 2928541

currently marketed docetaxel products. Provide us with your proposed plan for product launch to ensure medication errors between Docefrez and other docetaxel products are minimized.

C. Container Labels

1. Revise the statement "Each Docefrez for Injection..." to read as follows and use the recommended bolding:

   "Each Docefrez for Injection vial contains a slight overfill to deliver **20 mg of Docetaxel per 0.8 mL after reconstitution** (for the 20 mg vial)

   or

   "Each Docefrez for Injection vial contains a slight overfill to deliver **80 mg of Docetaxel (24 mg/mL after reconstitution)**"

2. Relocate the "Rx Only" statement to one of the side panels in order to make room for other statements on the principal display panel.

D. Carton Labeling

3. Add a banner to the principal display panel that states the following: "New Concentration and Preparation". Please note this statement must be removed after six months.

4. Add the "Each Docefrez for Injection vial..." statement to the principal display panel and position it below the route of administration (see comment C.1 above).

5. Relocate the "Rx Only" statement to a less prominent area on the principal display panel (e.g., lower left or right corner) and move the "Each carton contains…" information a little higher up on the principal display panel.

REFERENCES

Holmes, Loretta. Docefrez for Injection Label and Labeling Review, OSE Review 2009-983, dated February 19, 2010.

APPENDICES

Appendix A: Docetaxel Injection Indications of Use and Dosage Information

Indication of Use	**Dosage**
Breast cancer: locally advanced or metastatic	60 mg to 100 mg/m^2 single agent
(b) (4)	
Non-small cell lung cancer, after platinum therapy failure	75 mg/m^2 single agent
(b) (4)	
Hormone refractory prostate cancer	75 mg/m^2 with 5 mg prednisone twice a day continuously
Premedication Regimen	Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before administration. Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12 hours, 3 hours, and 1 hour before treatment

Appendix B: AERS Database ISR Report Numbers

Report	**ISR Number**
1	5316842
2	5338548
3	5403737
4	5455743
5	5490684
6	5581415
7	5621594
8	5684161
9	5744074
10	5788965
11	6082771
12	6134156
13	6221946
14	6392206
15	6607952
16	6611878
17	6673107
18	7033529
19	7092480
20	7153486
21	7206114
22	7206129
23	7206142
24	7235796
25	7241888
26	7270819
27	7355206

Reference ID: 2928541

Appendix C: Excluded AERS Search Results

The AERS search conducted on March 21, 2011 yielded 26 cases. Of these cases, 23 were excluded from further evaluation for the reasons below:

- Adverse drug reactions not related to a medication error (n=11)
- Taxotere was a concomitant medication and not involved in a medication error (n=6)
- Cases reported both an adverse drug reaction not related to a medication error and product quality complaint (n=4)
- Wrong route of administration. Foreign case (Germany). There was not enough information provided to evaluate the case. (n=1)
- Improper dose (overdose). The patient was in a study protocol and there was not enough information provided to evaluate the case. (n=1)

Appendix D: Container Labels

(b) (4)

Appendix F: Carton Labeling

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/s/

IRENE Z CHAN on behalf of LORETTA HOLMES
04/05/2011

IRENE Z CHAN
04/05/2011

CAROL A HOLQUIST
04/06/2011

Division of Drug Marketing, Advertisement, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Jamila Mwidau, Project Manager, Division of Drug Oncology Products, (DDOP)

From: Nisha Patel, Regulatory Review Officer
Zarna Patel, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications, (DDMAC)

CC: Karen Rulli, Group II Leader, DDMAC
Amy Toscano, Group IV Leader, DDMAC

Date: March 23, 2011

Re: Comments on draft labeling (Package Insert) for Docefrez (docetaxel) NDA 022534

In response to your consult dated January 12, 2011, we have reviewed the draft Package Insert and Patient Package Insert (PPI) for Docefrez, and offer the following comments. Note that DDMAC has made these comments using the version updated by FDA on March 17, 2011.

Package Insert Labeling:

Section	Statement from draft	Comment
12.1 Mechanism of Action	Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, **a feature which differs from most spindle poisons currently in clinical use.**	Is the bolded statement supported by substantial evidence? This statement is promotional in tone and could be used to support superiority claims over other agents.

Patient Package Insert:

Section	Statement from draft	Comment
17.2 FDA-Approved Patient Labeling	**What is DOCEFREZ?** DOCEFREZ is a prescription anti-cancer medicine used to treat certain people with: • breast cancer • non-small cell lung cancer • prostate cancer	This presentation broadens the indication by implying that Docefrez can be used as a single agent to treat prostate cancer, when such is not the case. According to the draft PI, "Docefrez in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer. In addition, this presentation broadens the indication by not conveying that for particular indications, Docefrez cannot be used as first line agent. For example, Docefrez should be used only after failure of prior chemotherapy for advanced or metastatic breast cancer and after failure or prior platinum-based chemotherapy for locally advanced or metastatic non-small cell lung cancer. We recommend revising the indication statement to be consistent with the PI, using consumer-friendly language.

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/s/

ZARNA PATEL
03/23/2011

NISHA J PATEL
03/23/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 19, 2010
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Kristina C. Arnwine, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	DMEPA Label & Labeling Review
Drug Name(s):	Docefrez (Docetaxel) for Injection 20 mg and 80 mg per vial
Application Type/Number:	NDA 022534
Applicant/sponsor:	Sun Pharma Global FZE
OSE RCM #:	2009-983

1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products (DDOP) for assessment of the Applicant's February 2, 2010 revisions to the container labels and carton labeling for Docefrez (Docetaxel) for Injection. These revisions were made in response to the Agency's January 27, 2010 label and labeling recommendations.

2 REGULATORY HISTORY

DMEPA met with the CMC review team on October 19, 2009 to discuss labels and labeling for this NDA (see Appendices C, D, and E). During the meeting, safety concerns with how the drug vial overfill and diluent vial overfill are communicated on the labels and labeling were identified. A follow up meeting was held on December 11, 2009 for further discussion on how this information can be safely presented and communicated in the labels and labeling to minimize confusion and promote the safe use of the product. As a result, CMC and DMEPA reached a consensus and our collective container label and carton labeling recommendations are in Appendix A. These recommendations were sent to the Applicant on January 27, 2010.

As a result of the recommendations made for the container labels and carton labeling, revisions to sections 2.7 (Handling and Preparation Precautions) and 2.8 (Preparation and Administration) of the insert labeling were necessary in order to ensure consistency between the container labels, carton and insert labeling (Appendix B). Final recommendations for these sections of the insert labeling were communicated to the Division during a Docefrez labeling meeting on February 17, 2010. Both DDOP and CMC concurred with our recommendations. The recommended changes were incorporated into the insert labeling and sent to the Applicant on February 19, 2010.

3 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton, and insert labeling submitted as part of the February 2, 2010 submission (see Appendices F, G, and H).

- Container Labels
    - Active drug (20 mg and 80 mg vials)
    - Diluent for the 20 mg and 80 mg active drug vials
- Carton Labeling (20 mg and 80 mg)

4 RECOMMENDATIONS

Our evaluation noted areas where information on the revised container labels and carton labeling can be improved to minimize the potential for medication errors. Our recommendations are provided in *Section 4.1 Comments to the Applicant*.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

4.1 COMMENTS TO THE APPLICANT

A. Container Labels

1. The statements "Warning: Cytotoxic Agent" and "Single-use vial—Discard Unused Portion" (b) (4) These are two separate statements so they should appear separate from each other.

2. Delete the statement "Discard Unused Portion" (b) (4) since it is already a part of the "Single-use vial..." statement.

B. Container Labels and Carton Labeling

In the sentence that begins: "Withdraw only the required...", delete the word (b) (4).

C. Carton and Insert Labeling

Revise the statement (b) (4) to read "Single-use vial". This will ensure consistency between all labels and labeling.

APPENDIX A

DMEPA AND CMC COMMENTS FORWARDED TO THE APPLICANT ON JANUARY 27, 2010

A. Carton Labeling, 20 mg

1. General Comments

   a. Revise the established name presentation as follows on all carton panels: place parentheses around the established name and relocate it below the proprietary name and next to the dosage form [i.e., "(Docetaxel) for Injection"]

   b. Change the statement of strength from (b) (4) to read: "20 mg*".

   c. Revise the route of administration statement (b) (4) to read: "For Intravenous Infusion Only", and use title case.

2. Principal Display Panel

   a. Delete the statement (b) (4) of the principal display panel.

   b. Replace the statement (b) (4) with the following:

      Each carton contains:
      One vial of Docefrez (docetaxel) for Injection 20 mg
      One vial of DILUENT for Docefrez 20 mg

3. Back Panel

   a. Add the statement of strength and route of administration.

   b. Revise the statement (b) (4) to read: "*Each Docefrez for Injection vial contains a slight overfill to deliver 20 mg of Docetaxel."

   c. Revise the statement (b) (4) to read: "Each DILUENT for Docefrez for Injection 20 mg vial contains 1.13 mL of 35.4% w/w ethanol in polysorbate 80"

   d. Replace the (b) (4) statement with the following wording:

      "Withdraw 1 mL of Diluent to reconstitute the Docefrez for Injection. Once reconstituted with 1 mL of Diluent, the resultant concentration is **20 mg/0.8 mL**."

"Withdraw only the required amount of the reconstituted solution needed to prepare the final infusion solution. See package insert for full dilution information".

"Discard Unused Portion."

Additionally, delete the word [redacted] from the statement and ensure that the resultant concentration (i.e., 20 mg/0.8 mL) is highlighted using a bold or contrasting color font.

e. The following statements are redundant and should be deleted:

[redacted]

4. Side panels

Delete the statement [redacted].

B. Carton Labeling, 80 mg

1. General Comments

a. Revise the established name presentation as follows on all carton panels: place parentheses around the established name and relocate it below the proprietary name and next to the dosage form [i.e., "(Docetaxel) for Injection"]

b. Change the statement of strength from [redacted] to read: "80 mg*".

c. Revise the route of administration statement [redacted] to read: "For Intravenous Infusion Only", and use title case.

2. Principal Display Panel

a. Delete the statement [redacted] of the principal display panel.

b. Replace the statement [redacted] with the following:

Each carton contains:
One vial of Docefrez (docetaxel) for Injection 80 mg
One vial of DILUENT for Docefrez 80 mg

3. Back Panel

a. Add the statement of strength and route of administration.

b. Revise the statement [redacted] to read: "*Each Docefrez for Injection vial contains a slight overfill to deliver 80 mg of Docetaxel."

c. Revise the statement [redacted] to read: "Each DILUENT for Docefrez for Injection 80 mg vial contains 4.21 mL of 35.4% w/w ethanol in polysorbate 80".

d. Replace the [redacted] statement with the following wording:

"Withdraw 4 mL of Diluent to reconstitute the Docefrez for Injection. Once reconstituted with 4 mL the resultant concentration is **24 mg/mL**."

"Withdraw only the required amount of the reconstituted solution needed to prepare the final infusion solution. See package insert for full dilution information."

"Discard unused portion."

Additionally, delete the word [redacted] from the statement and ensure that the resultant concentration (i.e., 24 mg/mL) is highlighted using a bold or contrasting color font.

e. The following statements are redundant and should be deleted:

[redacted]

4. Side panels

Delete the statemen [redacted].

C. Container Label, 20 mg vial

1. Revise the statement of strength [redacted] to read "20 mg" and use a larger font.

2. Revise the statement [redacted] to read: "For Intravenous Infusion Only", and use title case.

3. Add the following statements: Warning: "Cytotoxic Agent" and "Single use vial—Discard Unused Portion", if space allows. Consider removing the line graphic at the bottom of the label in order to provide more space to add these statements.

4. Delete the statement [redacted] and replace it with the following statement: "*Each Docefrez for Injection vial contains a slight overfill to deliver 20 mg of Docetaxel."

5. Increase the prominence of the proprietary name, established name and strength.

6. Relocate the established name to below the proprietary name as follows:

Docefrez
(docetaxel) for Injection

7. Replace the [redacted] statement with the following wording:

   "Withdraw 1 mL of Diluent to reconstitute the Docefrez for Injection**.** Once reconstituted with 1 mL of Diluent, the resultant concentration is **20 mg/0.8 mL**."

   "Withdraw only the required amount of the reconstituted solution needed to prepare the final infusion solution. See package insert for full dilution information".

   "Discard Unused Portion."

   Additionally, delete the word [redacted] from the statement and ensure that the resultant concentration (i.e., 20 mg/0.8 mL) is highlighted using a bold or contrasting color font.

D. Container Label, 80 mg vial

1. Revise the statement of strength [redacted] to read: "80 mg*".

2. Revise the statement [redacted] to read: "For Intravenous Infusion Only", and use title case.

3. Add the following statements: Warning: "Cytotoxic Agent" and "Single use vial—Discard Unused Portion", if space allows. Consider removing the line graphic at the bottom of the label in order to provide more space to add these statements.

4. Delete the statement [redacted] and replace it with the following statement: "*Each Docefrez for Injection vial contains a slight overfill to deliver 80 mg of Docetaxel."

5. Replace the [redacted] statement with the following wording:

   "Withdraw 4 mL of Diluent to reconstitute the Docefrez for Injection. Once reconstituted with 4 mL the resultant concentration is **24 mg/mL**."

   "Withdraw only the required amount of the reconstituted solution needed to prepare the final infusion solution. See package insert for full dilution information."

   "Discard unused portion."

   Additionally, delete the word [redacted] from the statement and ensure that the resultant concentration (i.e., 24 mg/mL) is highlighted using a bold or contrasting color font.

E. Diluent for 20 mg vial

1. Revise the statement [redacted] to read "DILUENT for Docefrez 20 mg". Ensure the word "DILUENT" is the most prominent and the only word presented in all caps.

2. Delete the statement [redacted] in order to prevent the diluent vial from being confused as the active drug vial. Add a net quantity statement (i.e., "1.13 mL") in this location.

3. Revise the statement [redacted] to read: "Each vial contains 1.13 mL of 35.4% ethanol in polysorbate 80".

4. Revise [redacted] to "Withdraw 1 mL of Diluent to reconstitute the contents of the Docefrez 20 mg vial. See package insert for full dilution information." Delete the word [redacted] from the statement.

5. Add the statement "Single Use Vial—Discard Unused Portion".

F. Diluent for 80 mg vial

1. Revise the statement [redacted] to read: "DILUENT for Docefrez 80 mg". Ensure the word "DILUENT" is the most prominent and the only word presented in all caps.

2. Delete the statement [redacted] in order to prevent the diluent vial from being confused as the active drug vial. Add a net quantity statement (i.e., "4.21 mL") in this location.

3. Revise the statement [redacted] to read: "Each vial contains 4.21 mL of 35.4% ethanol in polysorbate 80".

4. Revise [redacted] to "Withdraw 4 mL of Diluent to reconstitute the contents of the Docefrez 80 mg vial. See package insert for full dilution information." Delete the word [redacted] from the statement.

5. Add the statement "Single Use Vial—Discard Unused Portion".

Appendix B: Insert Labeling Comments

Sections 2.7 Handling and Preparation Precautions and 2.8 Preparation and Administration

A. Revise all references to (b) (4) and (b) (4) to "reconstituted solution" and "infusion solution" respectively.

B. Revise table 3 as follows in order to ensure that the concentrations in the insert correspond with the concentrations on the container label and carton labeling.

Product	Fill Range of the Diluent (35.4% w/w ethanol in polysorbate 80)	Volume of Diluent to be added for the reconstitution	Concentration of the reconstituted solution
Docetaxel 20 mg vial	1.10 – 1.15 mL	1 mL	20 mg/0.8 mL
Docetaxel 80 mg vial	4.13 – 4.29 mL	4 mL	24 mg/mL

C. In section 2.8, #2, revise the statements of concentration to read as follows: For the 20 mg vial, the resultant concentration is 20 mg/0.8 mL. For the 80 mg vial, the resultant concentration is 24 mg/mL.

Appendix C: Container Labels (20 mg and 80 mg Active Drug Vials), not to scale

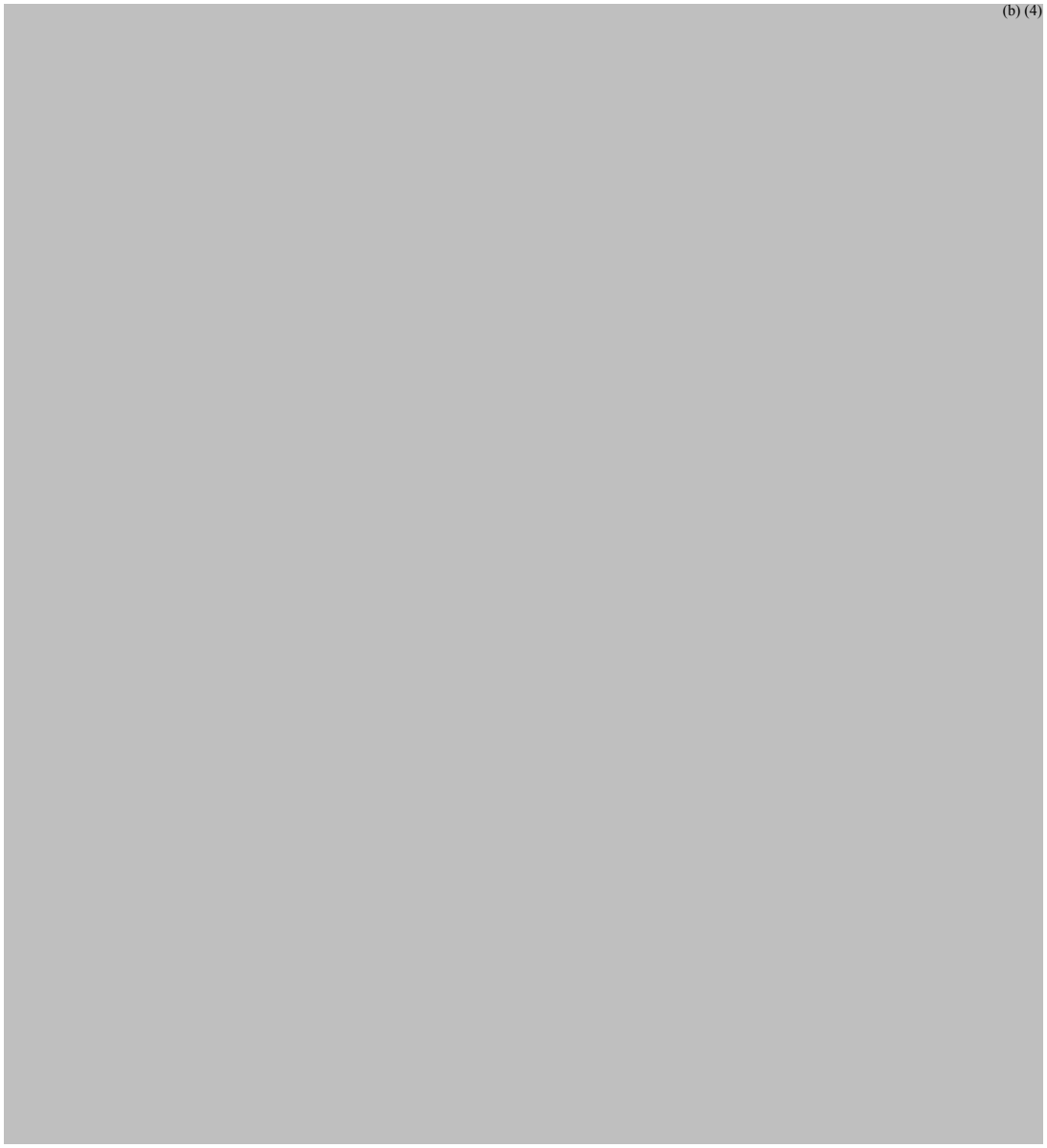
Appendix D: Container Labels (Diluent for 20 mg and 80 mg active drug vials), not to scale

Appendix E: Carton Labeling (20 mg and 80 mg), not to scale

Appendix F: Revised Container Labels (20 mg and 80 mg Active Drug Vials), not to scale

Appendix G: Revised Container Labels (Diluent for 20 mg and 80 mg active drug vials), not to scale

Appendix H: Revised Carton Labeling (20 mg and 80 mg), not to scale



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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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/s/

LORETTA HOLMES
02/19/2010

KRISTINA C ARNWINE
02/19/2010

DENISE P TOYER
02/22/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum: Internal Labeling Consult

Date: February 16, 2010

To: Alberta Davis-Warren, Project Manager, DDOP
Qin Ryan, Medical Review, DDOP

From: Keith Olin, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA # 22-534
DDMAC PI labeling comments for DOCEFREZ (docetaxel) for injection

---

DDMAC has reviewed the proposed PI for Docefrez (docetaxel) for injection submitted for consult by the Division of Drug Oncology Products, and offers the following comments. Comments regarding the proposed PPI will be provided separately by Sheetal Patel.

The version of the draft PI used in this review was sent via email on February 11, 2010.

HIGHLIGHTS

----------ADVERSE REACTIONS----------
Most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia (6)

Comment [ko1]: DDMAC: Need to include the percent incidence rates for the most common adverse events list in the highlight section of the PI It minimizes the risks associated with DOCEFREZ See regulation

5.2 Hepatic Impairment
Patients with combined abnormalities of transaminase and alkaline phosphatase should, (b) (4) not be treated with Docefrez *[see Boxed Warning, Use in Specific Populations (8.6),Clinical Pharmacology (12.3)]*.

(b) (4)

8.6 Hepatic Impairment
Patients with bilirubin > ULN should generally not receive docetaxel. Also, patients with AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should (b) (4) not receive docetaxel. *[see Boxed Warning, Warnings and Precautions, (5.2), Clinical Pharmacology (12.3)]*.

6.1 Clinical Trials Experience

Breast Cancer

Monotherapy with docetaxel for locally advanced or metastatic breast cancer after failure of prior chemotherapy

Docetaxel 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to docetaxel. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving docetaxel for the treatment of breast cancer and in patients with other tumor types (See Table 4).

Table 4- Summary of Adverse Reactions in Patients Receiving Docetaxel at 100 mg/m^2

Table 6- Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at Docetaxel 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Comment [ko3]: DDMAC: Tables 4 and 6 include the incidences of AE's as "any" and "severe" in the tables DDMAC recommends defining "any" and "severe" either before the tables or within the tables (e g – severe = grade 3 and 4)

14 Clinical Studies

14.1 Locally Advanced or Metastatic Breast Cancer

The efficacy and safety of docetaxel have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens).

Comment [ko4]: DDMAC recommends including a sentence stating what the secondary endpoints (if applicable) were for each trial following the primary endpoint sentences

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with docetaxel (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). 203 patients were randomized to docetaxel and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the docetaxel arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results (See Table 12).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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/s/

KEITH J OLIN
02/22/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: February 17, 2010

To: Alberta Davis-Warren RPM/OODP/DDOP

From: Sheetal Patel, PharmD, DDMAC

Re: NDA # 22-534
DOCEFREZ (docetaxel) for Injection

As requested in your consult dated June 4, 2009, DDMAC has reviewed the draft labeling for DOCEFREZ (docetaxel) for Injection. DDMAC's comments are based on the proposed version of the labeling titled "SC PI from RD 22Jan10.doc" from January 22, 2010.

DDMAC's comments are provided directly in the attached marked-up copy of the labeling. Comments regarding the proposed PI will be provided separately by Keith Olin.

If you have any questions about DDMAC's comments on the PPI please contact Sheetal Patel at 6-5167 or at Sheetal.Patel@fda.hhs.gov.

39 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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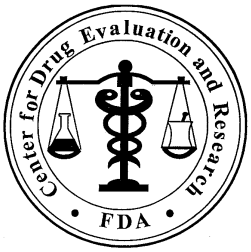
/s/

SHEETAL PATEL
02/17/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 2, 2010
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Through:	Mary Willy, PhD, Deputy Director Division of Risk Management (DRISK) Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer, Acting Team Leader Division of Risk Management
From:	Melissa I. Hulett, RN, BSN, MSBA Patient Labeling Reviewer Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Docefrez (docetaxel) for Injection
Application Type/Number:	NDA 22-534
Applicant/sponsor:	Sun Pharma Global FZE, c/o Salamandra, LLC
OSE RCM #:	2009-2380

1 INTRODUCTION

Salamandra, LLC, U.S. agent for Sun Pharma Global FZE, submitted an original 505 (b) (2) New Drug application, NDA# 22-534, for Docefrez (docetaxel) for Injection on April 23, 2009. Taxotere (docetaxel) Injection Concentrate, is the Reference Listed Drug.

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Docefrez docetaxel) for Injection. DDOP identified the tentatively approved PI and PPI for Hopsira, Inc's Docetaxel (docetaxel) Injection, as the comparator for DRISK to use in the current review.

Please let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Docefrez (docetaxel) for InjectionPrescribing Information (PI) submitted April 23, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on January 22, 2010 and January 27, 2010.
- Draft Docefrez (docetaxel) for injection Patient Package Insert (PPI) submitted April 23, 2009, revised by the review division throughout the review cycle, and provided to DRISK on January 22, 2010 and January 27, 2010.

3 DISCUSSION

In our review of the PPI, we have:

- used the PPI provided on January 22, 2010 as the base document for our review and incorporated changes, as appropriate, from the review division PPI further revised on January 27, 2010.
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 RESULTS OF REVIEW

1. Our revisions to the PPI reflect DRISK's current practices regarding the content and format for patient labeling. We recommend revising the currently approved PPI for Taxotere (docetaxel) Injection Concentrate and the tentatively approved PPI for Docetaxel (docetaxel) Injection to be consistent with the recommended changes in this review. The paragraph format used in the sponsor submitted PPI is not patient friendly. We reformatted it using principles that enhance cognition, such as good use of white space, chunking, and use of bullets.
2. The revised PPI dated January 27, 2010, references both docetaxel and Docefrez throughout the document. Docefrez should be used throughout the text in the PPI except in the second line of the heading where the established name is listed in parentheses. We have updated the PPI where appropriate.
3. The review division should consult the SEALD team regarding section numbering. It is our understanding that patient labeling no longer is assigned a sub-section number in section 17; rather, it follows at the end of section 17. Also, confer with SEALD regarding acceptable placement of the comment regarding the PPI: (b) (4) Such statements generally do not go on the PPI itself. It seems that such statement should go at the beginning of section 17 where there is usually mention of FDA-approved patient labeling so that the pharmacist will not that there is information for patients.

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

12 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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/s/

MELISSA I HULETT
02/02/2010

MARY E WILLY
02/02/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 022534 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Docefrez
Established Name: Docetaxel
Strengths: 20 mg/vial and 80 mg/vial Injection

Applicant: Sun Pharma Global FZE
Agent for Applicant (if applicable): Salamandra, LLC

Date of Application: April 23, 2009
Date of Receipt: April 23, 2009
Date clock started after UN: N/A
Date of Filing Meeting: June 5, 2009
Filing Date: June 23, 2009
Action Goal Date (optional): February 23, 2010 User Fee Goal Date: February 23, 2010

Indication(s) requested: treatment of Breast cancer, non-small cell lung cancer, prostate cancer (b) (4)

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: (Taxotere NDA 20-449 is currently the only approved docetaxel product in the United States.

Exclusivity Code	Expiration
I-490	March 22, 2009
I-543	September 28, 2010
I-519	October 17, 2009
I-542	September 28, 2010

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B. new appendix B

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☒
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☐ NO ☒
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: (b) (4)

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 24, 2008 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

●	Did applicant request categorical exclusion for environmental assessment?	YES	☒	NO	☐
	If no, did applicant submit a complete environmental assessment?	YES	☐	NO	☐
	If EA submitted, consulted to EA officer, OPS?	YES	☐	NO	☐
●	Establishment Evaluation Request (EER) submitted to DMPQ?	YES	☒	NO	☐
●	If a parenteral product, consulted to Microbiology Team? YES		☒	NO	☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 5, 2009

NDA #: 22-534

DRUG NAMES: Docefrez (docetaxel)

APPLICANT: Sun Pharma Global FZE

BACKGROUND: Docetaxel is a cytotoxic antimicrotubule agent, it belongs to the taxoid class of chemotherapy drugs and is a clinically well established antineoplastic medication. Taxotere® is the Reference Listed Drug (RLD). It was first approved for use in locally advanced or metastatic breast cancer after failure of prior anthracycline chemotherapy. Since then, it has been approved for several other uses, both as monotherapy and as part of combination regimens. The sponsor proposes docetaxel for the treatment of breast cancer, non-small cell lung cancer, prostate cancer (b) (4).

ATTENDEES: Robert Justice, V. Ellen Maher, Anthony Murgo, Qin Ryan, Deborah Mesmer, Young-Jin Moon, Alex Putman, Hari Sarker

ASSIGNED REVIEWERS (including those not present at filing meeting): Qin Ryan, Margaret Brower, Debasis Ghosh, John Metcalfe, Keith Olin, and Stephanie Victor

Discipline/Organization	Reviewer
Medical:	Qin Ryan
Secondary Medical:	Ellen Maher
Statistical:	N/A
Pharmacology:	Margaret Brower
Statistical Pharmacology:	
Chemistry:	Debasis Ghosh
Environmental Assessment (if needed):	
Clinical Pharmacology:	Young-Jin Moon
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Alberta Davis-Warren
Other Consults:	DDMAC
	Micro

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: No clinical studies
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☒

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

CLINICAL PHARMACOLOGY FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Alberta E. Davis-Warren
Regulatory Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERTA E DAVIS WARREN
02/01/2010

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22534/000	**Sponsor:**	SUN PHARMA GLOBAL
Code:	150		4800 HAMPDEN LANE STE 900
Priority:	5S		BETHESDA, MD 20814
Stamp Date:	23-APR-2009	**Brand Name:**	DOCEFREZ INJECTION (20/80 MG/VIAL)
PDUFA Date:	03-MAY-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	DOCETAXEL INJECTION (20/80MG/VIAL)
District Goal:	25-DEC-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; INJECTABLE; DOCETAXEL; 20MG 002; INJECTABLE; DOCETAXEL; 80MG	

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	D. GHOSH	Review Chemist	(HFD-150)	301-796-4093
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation: ACCEPTABLE on 05-JUN-2009 by M. STOCK (HFD-320) 301-796-4753

Establishment: **CFN:** (b) (4) **FEI:** (b) (4) (b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-JUN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Reference ID: 2955024

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9611130 **FEI:** 3002809586		
	SUN PHARMACEUTICAL INDUSTRIES LTD HALOL-BARODA HWY HALOL-389350		
	HALOL, GUJARAT STATE (BARODA), , INDIA		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	SMALL VOLUME PARENTERAL, LYOPHILIZED	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-JUN-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Reference ID: 2955024

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22534/000	**Action Goal:**	
S Date:	23-APR-2009	**District Goal:**	25-DEC-2009
Regulatory:	23-FEB-2010		
Applicant:	SUN PHARMA GLOBAL	**Brand Name:**	DOCEFREZ INJECTION (20/80 MG/VIAL)
	4800 HAMPDEN LANE STE 900	**Estab. Name:**	
	BETHESDA, MD 20814	**Generic Name:**	DOCETAXEL INJECTION (20/80MG/VIAL)
Priority:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150		

Application Comment: THE CONTACT PERSON FOR THE APPLICATION IS KARIN KOOK, 301-652-6110 (on 29-MAY-2009 by D. HENRY () 301-796-4227)

THIS IS A 505 (B)(2) APPLICATION. RLD IS TAXOTERE (on 20-MAY-2009 by D. HENRY () 301-796-4227)

FDA Contacts:				
	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	D. GHOSH	Review Chemist	(HFD-150)	301-796-4093
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:	ACCEPTABLE	on 05-JUN-2009	by M. STOCK	(HFD-320)	301-796-4753

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4) **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Estab. Comment: THE ADDRESS LISTED IN THE APPLICATION FOR THIS ESTABLISHMENT VARIES SLIGHTLY FROM OUR DATABASE. ITS LISTED AS: (b) (4)
(on 29-MAY-2009 by D. HENRY () 301-796-4227)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	29-MAY-2009				HENRYD
OC RECOMMENDATION	01-JUN-2009			ACCEPTABLE BASED ON PROFILE	STOCKM

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611130 **FEI:** 3002809586

SUN PHARMACEUTICAL INDUSTRIES LTD

HALOL-BARODA HWY HALOL-389350
HALOL, GUJARAT STATE (BARODA), , INDIA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: THE APPLICATION LISTS THE CFN/EIN NUMBER FOR THIS ESTABLISHMENT AS 3003789481. (on 29-MAY-2009 by D. HENRY () 301-796-4227)
ADDITIONAL CONTACT NUMBERS ARE: 91-22 28212115; 91-22 28212128 (on 20-MAY-2009 by D. HENRY () 301-796-4227)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	29-MAY-2009				HENRYD
SUBMITTED TO DO	01-JUN-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	05-JUN-2009			ACCEPTABLE BASED ON FILE REVIEW	STOCKM
OC RECOMMENDATION	05-JUN-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

APPEARS THIS WAY ON ORIGINAL